Stereocontrolled synthesis of 2-azido and 2-*N*-acetylamino-2-deoxy-β-D-C-glycosides from the corresponding lactones

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The reaction of perbenzylated 2-azido-2-deoxy-D-hexono-1,5-lactones with organometallic reagents followed by reduction provides a new stereocontrolled synthesis of 2-azido-2-deoxy-β-D-C-glycosides, which can be efficiently transformed into 2-*N*-acetylamino-2-deoxy-β-D-C-glycosides.

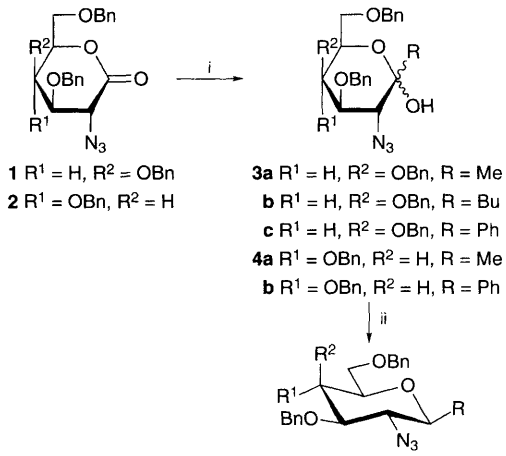
As a part of a continuing programme on C-glycosides synthesis,[1] we describe herein an efficient method for the synthesis of 2-azido-2-deoxy-β-D-C-glycopyranosides from the corresponding lactones.

In the recent years, considerable effort has been devoted to the synthesis of C-glycosides[2] owing to their biological interest and synthetic utility, and many methods are now available for the stereocontrolled preparation of α and β anomers.[3] Despite the importance of 2-amino-2-deoxy-sugars in biological systems such as aminoglycoside antibiotics[4] and antigenic determinants on cell surfaces,[5] the synthesis of their C-glycosides analogues is less well documented. Several groups have transformed D-glucosamine derivatives into an α/β mixture of C-glycosides by a Wittig-type reaction followed by cyclisation.[6] The resulting stereocontrol depends on the starting carbohydrate derivative and on the protecting groups employed. Direct alkylation of 2-*N*-acetylamino-2-deoxy-D-glucopyranosyl chloride with potassium diethylmalonate followed by decarboxylation furnished β-isomer of amino C-glycoside.[7] Reaction of an arabinofuranosyl benzylamine derivative with vinylmagnesium bromide followed by mercuriocyclisation afforded methyl α-D-C-glycoside of D-glucosamine.[8] In addition, the direct coupling of aldehydes with a glycosyl anion has recently been reported for the preparation of α- or β-D-C-glycosides of D-glucosamine.[9]

Since the azido group is a good synthetic equivalent of the amino group, 2-azido-2-deoxyglycopyranosides were employed as starting material for the synthesis of C-glycosyl derivatives bearing a cyano group[10] or an alkynyl chain[11] at the anomeric centre, and mixtures of anomers were obtained. The compatibility of the azido group with Lewis acids allowed the stereocontrolled introduction of an allyl chain at C-1 leading to α-D-C-glycosides.[12]

Since condensation of an organolithium derivative to a protected lactone followed by reduction of the obtained aldol gave good results for the preparation of β-D-C-glycopyranosides to us[13] and others,[14] we decided to evaluate this methodology for the preparation of 2-azido-2-deoxy-β-D-C-glycopyranosides and we report herein our results. 2-Azido-2-deoxy-D-*galacto*-hexono-1,5-lactone **1**[15] and its *gluco* **2**[15] isomer obtained by oxidation of the corresponding lactol[16] were employed in this study.

Reaction of **1** or **2** with 1.1 equiv. of an organolithium derivative at −78 °C afforded the corresponding aldol in good yield (Table 1). Compounds **3a–c** and **4a** were directly reduced



1 R^1 = H, R^2 = OBn
2 R^1 = OBn, R^2 = H

3a R^1 = H, R^2 = OBn, R = Me
b R^1 = H, R^2 = OBn, R = Bu
c R^1 = H, R^2 = OBn, R = Ph
4a R^1 = OBn, R^2 = H, R = Me
b R^1 = OBn, R^2 = H, R = Ph

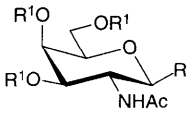
5a R^1 = H, R^2 = OBn, R = Me
b R^1 = H, R^2 = OBn, R = Bu
c R^1 = H, R^2 = OBn, R = Ph
6a R^1 = OBn, R^2 = H, R = Me
b R^1 = OBn, R^2 = H, R = Ph

Scheme 1 *Reagents and conditions*: i, RLi (1.1 equiv.), toluene, −78 °C, 1 h; ii, Et_3SiH (5 equiv.)–$BF_3{\cdot}Et_2O$ (6 equiv.), MeCN, −40 °C, 15 min

Table 1 Reaction of lactones **1** and **2**

Entry	Starting lactone	RLi	Aldol [yield (%)]	β-C-glycoside [yield[a] (%)]	H-1 (^{1}H NMR) δ	H-1 (^{1}H NMR) $J_{1,2}$/Hz
1	**1**	MeLi	**3a** [90]	**5a** [86.5]	3.01–3.16	9.50
2	**1**	BuLi	**3b** [89.5]	**5b** [84]	2.90–3.00	9.07
3	**1**	PhLi	**3c** [85.4]	**5c** [91]	3.92	9.30
4	**2**	MeLi	**4a** [85.4]	**6a** [66.5]	3.40–3.45	9.40
5	**2**	PhLi	**4b** [87.6]			

[a] Yield of isolated C-glycoside after purification by flash chromatography.



7a R^1 = Bn, R = Me
b R^1 = Bn, R = Bu
c R^1 = Bn, R = Ph
8c R^1 = H, R = Ph
9c R^1 = Ac, R = Ph

with triethylsilane in the presence of $BF_3{\cdot}Et_2O$.[17] Contrary to our previous result with the perbenzylated lactone,[13] the reduction was not possible with one equivalent of Lewis acid. A large excess of reagents was necessary (5 equiv. of Et_3SiH and 6 equiv. of $BF_3{\cdot}OEt_2$). In this case the reaction was finished in 15 min at −40 °C in acetonitrile and the β-D-C-glycoside was isolated in high yield (entries 1 to 4, Table 1).† The β configuration at the anomeric position was confirmed by the observed large coupling constant values between H-1 and H-2 (in the range of 9.07 to 9.50 Hz in $CDCl_3$) in the ^{1}H NMR spectra. However, in the case of compound **4b** (entry 5), no reduction was possible whatever the quantities of reagents, the times and the reaction temperature used.

The possibility of further transformation of these 2-azido-2-deoxy-C-glycosides was exemplified by the *galacto* derivatives. Reduction of the azido group was possible without cleavage of the benzyl groups by reaction with molecular hydrogen in the presence of Raney nickel and acetic anhydride. The *N*-acetyl derivatives **7a–c** were obtained in good yield as crystals.‡

Hydrogenolysis of the benzyl groups (H_2, Pd–C in THF) of **7c** proceeded smoothly and the C-glycosyl derivative of D-galactosamine **8c** was obtained in 89% yield. Acetylation of the hydroxy groups under classical conditions afforded the crystalline derivative **9c** in 91% yield which allowed further confirmation of the anomeric stereochemistry by ^{1}H NMR spectroscopy.§

In conclusion, we have developed an efficient method for the preparation of β-D-C-glycosides of *N*-acetyl-D-galacto- and -gluco-samine starting from readily available perbenzylated 2-azido-2-deoxyglycono-1,5-lactones.

Footnotes

† All compounds gave satisfactory analytical and spectral data.
‡ *Selected data* for **7a**: (74%), mp 124–125 °C, $[\alpha]_D$ +12.1 (*c* 1 in CH_2Cl_2). For **7b** (87%), mp 143–144 °C, $[\alpha]_D$ +24.3 (*c* 1 in CH_2Cl_2). For **7c** (75%), mp 168–169 °C, $[\alpha]_D$ +24.3 (*c* 1 in CH_2Cl_2).
§ *Selected data* for **9c**: mp 92–93 °C, $[\alpha]_D$ −12.4 (*c* 1 in CH_2Cl_2), ^{1}H NMR ($CDCl_3$) δ 4.37 (1 H, d, $J_{1,2}$ 10.2 Hz, H-1).

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Received, 17th October 1995; Com. 5/06872J